REMARKS

Reconsideration and allowance are respectfully requested.

Claims 28-67 and 71-72 are pending. Basis for new claims 71-72 can be found, inter alia, at page 10, lines 29-37, and page 16, lines 11-16, of the specification. Thus, no new matter is added by their entry. If the Examiner should disagree, however, she is respectfully requested to point out the challenged limitation with particularity in the next Action so support may be cited in response.

35 U.S.C. 112 – Definiteness

Claims 68-70 were rejected under Section 112, second paragraph, as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse because cancellation of claims 68-70 moots this rejection.

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 103 – Nonobviousness

To establish a case of prima facie obviousness, all of the claim limitations must be taught or suggested by the prior art. See M.P.E.P. § 2143.03. Obviousness can only be established by combining or modifying the prior art teachings to produce the claimed invention if there is some teaching, suggestion, or motivation to do so found in either the references themselves or in the knowledge generally available to a person of ordinary skill in the art. See, e.g., *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941, 1943-44 (Fed. Cir. 1992). It is well established that the mere fact that references can be combined does not render the resultant combination obvious unless the desirability of that combination is also taught or suggested by the prior art. See *In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990). Thus, even if all elements of the claimed invention were known, this is not sufficient by itself to establish a prima facie case of obviousness without some evidence that one would have been motivated to combine

those teachings in the manner proposed by the Examiner. See *Ex parte Levengood*, 28 USPQ2d 1300, 1302 (B.P.A.I. 1993).

Claims 28-70 were rejected under Section 103(a) as allegedly unpatentable over Fondy et al. (EP 0297946) in view of Richman et al. (J. Biol. Resp. Mod. 9:570-575, 1990) taken together with Lane et al. (WO 94/12202). Applicants traverse.

The document of Fondy et al. (EP 0297946, hereinafter "Fondy") discloses pharmaceutical compositions comprising a cytochalasin, preferably cytochalasin B, alone or in combination with an antineoplastic agent (chemotherapeutic agent), preferably doxorubicin. A synergistic effect of the two compounds in combination is claimed. But it is clear from page 7, lines 13-16, of Fondy that the two compounds were administered either concomitantly as a mixture or sequentially according to a schedule with the antineoplastic agent initially administered and then, 5 to 30 minutes later, the cytochalasin is administered. This schedule of administration is confirmed by the examples of Fondy. Example 15 shows the simultaneous administration of the two compounds. Example 16-18 show sequential administration in which the antineoplastic agent ADR (doxorubicin) is given first, and then the protective agent CB is given 5 to 30 minutes later. Moreover, it is stressed on lines 33-35 of Example 16 that sequential administration is essential to obtain synergy. Therefore, Fondy not only does not suggest the treatment schedule of the claimed invention but, on the contrary, Fondy suggests just the opposite.

The failure of Fondy to disclose the claimed invention is not remedied by the attempt to modify that disclosure with the other two cited documents.

The document Richman et al. (J. Biol. Resp. Mod. 9:570-575, 1990, hereinafter "Richman") discloses the alleged ability of interferon (INF) to protect normal human granulocyte/macrophage colony forming cells (CFU-GM) from Ara-C cytotoxicity. It was reported that a one-hour incubation of normal CFU-GM with alpha, beta, or gamma INF followed by a three-hour exposure to Ara-C increased the survival of normal cells. While admitting that the mechanism of action was unknown, Richman hypothesized IFN blockade of murine cell cycle progression in the G_0/G_1 phase and concluded, "If IFN preferentially blocks cycle progression in normal cells, it may be ideal for combining with cycle-active drugs [i.e., Ara-C] to improve selective toxicity for malignant cells" (page

570, right-hand column). But under the "Results" heading, Richman made plain that if the incubation time with IFN increases beyond one hour, the cytotoxicity of IFN also increases and the sub-sequent exposure to Ara-C results in a decrease of normal CFU-GM survival (page 572, last paragraph of the right-hand column). This was also illustrated in Table 1, which clearly shows that a 4 hour- or a 21 hour-incubation strongly decreases, in a dose-dependent manner, the survival of normal cells. It was concluded, "With long-term exposure to interferon, cytotoxicity did increase, but for both normal and malignant progenitors, and differential protection of normal colony-forming cells was no longer observed" (page 573, right-hand column). This represents a clear limitation on the protection of normal cells which was disclosed by Richman.

Applicants maintain that the present invention is characterized by a number of differences over Richman, which imply unexpected advantages as discussed below.

a) First, IFN is not envisioned as a protective compound in the present invention. Richman alleged a possible explanation for the observed protective effect of IFN: i.e., its ability to block cell cycle progression in the G_0/G_1 phase. These speculations, however, are contradicted by the facts reported in the same document. Namely that if incubation with IFN is longer than one hour, the protective effect is lost. On the basis of this hypothesis, one of ordinary skill in the art would have concluded either that the theory that IFN stably blocked the cell cycle in G_0/G_1 was incorrect or that the block in G_0/G_1 did not protect normal cells because, should the hypothesis prove correct, the longer the incubation, the higher would be the number of cells in G_0/G_1 and the better the protection.

Therefore, there would not have been a reasonable expectation of success to make the combination proposed on page 3 of the Action. One of ordinary skill in the art, having evaluated the experimental results reported in Richman, rather than the asserted hypothesis which was shown to be incorrect, would have found no suggestion to investigate compounds for their ability to block the cell cycle in G_0/G_1 phase and no motivation to block cytodieresis of normal cells. There is also no teaching or suggestion to replace Richman's IFN with one of Applicants' protective compounds.

b) The pre-treatment with the protective compounds of the present invention may be carried out for many hours (e.g., 24 or 48 hours) without affecting their protective

effect. Example 3 of the present specification, for instance, reports a pre-treatment of 24 hours. This possibility represents a further advantage of Applicants' invention over the method disclosed by Richman, who reports that incubation with IFN for more than one hour (i.e., 4 hours or 21 hours) increases the cytotoxicity of IFN and abolishes the protective effect on normal cells treated with Ara-C (page 572, right-hand column, and page 573, right-hand column).

Because protection occurs when the cell cycle of normal cells is blocked in the G_0/G_1 phase (i.e., inhibition of cytodieresis) and the normal cells are well known not to be synchronized, it would be immediately evident to one of ordinary skill in the art that the short incubation times suggested by Richman will, at best, protect only a limited number of cells, namely those cells entering the G_0/G_1 phase during the period of one hour. On the contrary, a pre-treatment with the protective compounds of Applicants' invention may run for as many hours as a complete cell cycle, or even more, without affecting protection. The clear result is that a much higher percent of normal cells, even all, will be protected by Applicants' invention.

c) The method according to Applicants' invention exploits the ability of a class A protective compound to protect normal cells by inducing a reversible block of cell cycle in G_0/G_1, through the inhibition of cytodieresis, in a p53-dependent manner, and finds application in the treatment of malignant cells having an inactive p53 pathway (see Examples 1 and 2 of Applicants' specification). This feature represents a criterion for discriminating between the pathological conditions in which protection is to be expected from those in which no protection occurs. This is a further advantage over Richman which, not recognizing the importance of the p53 pathway, did not give any teaching or suggestion to one of ordinary skill in the art as to which pathologies may be treated.

From the foregoing, it is clear that Applicants' invention relates to a method which is unexpectedly <u>improved</u> over the method disclosed by the cited documents. Such an improvement, which is due to the use of a reversible inhibitor of cytodieresis, such as a cytochalasin (except Cytochalasin B), jasplakinolide, chondramide, isoindolinone, or latrunculine, was neither taught nor suggested by Fondy or Richman. As such, the claimed invention cannot be regarded as obvious over the cited prior art.

Lane et al. (WO 94/12202) hereinafter "Lane"

Most tumor cells lack a functional p53 pathway. The Examiner alleged that mutation of p53 is a very common genetic alteration in human cancers as reported in Lane. She concluded that "these claims would be appropriate for almost any tumor model" (page 4 of the Action). In other words, the Examiner implicitly maintains that this feature does not contribute to the inventive merit of the claimed subject matter. Lane, however, describes p53 mutations which are not said to inactivate the p53 pathway but, on the contrary, simply result in mutant forms defective in specific functions, such as non-specific or sequence-specific DNA binding, and transcriptional activation (see page 3, first paragraph, of Lane). Therefore, the allegations in the Action are unsupported by the evidence of record.

It must be stressed that inactivity of the p53 pathway is simply a technical pre-condition necessary to the successful outcome of the treatment. The claimed method is patentable because the specific sequence of procedural steps as recited in the claims allowing selective protection of proliferating, p53-proficient normal cells and eradication of proliferating, p53-defective tumor cells would not have been obvious to one of ordinary skill in the art at the time that Applicants made their invention. For this reason, the claimed invention is not made obvious by Lane, which focuses on a different approach.

Applicants have highlighted the patentability of their invention and the principle underlying it through the above discussion. The cited documents, taken alone or in combination, do not render obvious the claimed invention. Since the pending claims are based on this principle, they should all be recognized as not being obviously derivable from the cited prior art. In particular, it is stressed that neither Fondy nor Richman relate to exploiting the inactivation of the p53 pathway in reducing the side effects of chemotherapy of cancer or an infection caused by microorganisms. For this reason, claims 52-53 and claims dependent thereon should also be recognized as patentable.

Finally, the cited documents neither teach nor suggest pharmaceutical compositions or kits. Moreover, they are silent on pharmaceutical compositions and kits which are designed to initially release the protective compound, and subsequently release

both protective and chemotherapeutic compounds. In claim 58, there is a composition of both compounds characterized by delayed release: i.e., the protective compound is released prior to release of the chemotherapeutic compound (see Fig. 1 of Applicants' specification). In claim 63, the kit provides sequential administration with the protective compound alone followed by both protective and chemotherapeutic compounds. For this reason, claims 58 and 63 and claims dependent thereon should also be recognized as patentable.

It was alleged with regard to the time of pre-treatment or treatment, which is recited in some of the pending claims but is neither taught nor suggested in the cited prior art, that "one skilled in the art would find it obvious in view of routine optimization" (see page 4 of the Action). But no evidence was cited in the Action to support the Examiner's allegation that these are matters of routine optimization. If this portion of the rejection is maintained, Applicants respectfully request that such evidence be provided.

Withdrawal of the Section 103 rejection is requested because the invention as claimed would not have been obvious to a person of ordinary skill in the art at the time it was made.

Conclusion

Having fully responded to all of the pending rejections contained in this Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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